Advanced Pharmaceutical Technology

Modified Release Oral Drug Delivery Systems

Suhair Sunoqrot, PhD
Associate Professor of Pharmaceutics
Faculty of Pharmacy
Al-Zaytoonah University of Jordan

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Modified release

- Manipulation or modification of drug release from the dosage form by delivering the API at:
  - A desired rate (extended, sustained, prolonged, controlled release dosage forms)
  - Pre-defined time points (pulsatile release dosage forms)
  - Specific sites in the GIT (delayed release, gastro-resistant dosage forms)
- The need for developing MR dosage forms came as a result of an improved understanding of the relationship between clinical pharmacology and physiology and biological conditions

Therapeutic benefits

1. Improved efficacy by maintaining the drug within the therapeutic range for longer or timing drug release to occur when it is required
2. Reducing adverse effects
3. Improved patient compliance
4. Increased selectivity

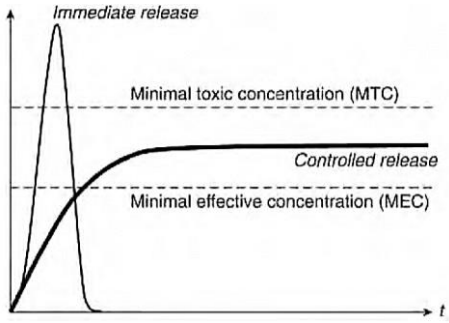
- **Commercial advantages:**
  1. Product differentiation/ line extension
  2. Market expansion
  3. Increased cost effectiveness

Strategies to modify drug release

1. Extended release (zero-order, first-order, biphasic)
2. Delayed release (enteric-coated, colon targeted)
3. Programmed release (pulsatile, delayed-extended)

Oral extended release systems

- Various physical and chemical approaches have been successfully applied to produce well-characterized delivery systems that extend drug release into the GI tract
- Currently, most ER technologies are based on polymeric systems



Oral extended release systems

- Key considerations: drug solubility and permeability
  - BCS classes I and III drugs are more suitable than II and IV for an extended release system (why?)
- Another factor to consider is drug half-life ($t_{1/2}$ 4 – 6 h), and required dose (affects tablet size)

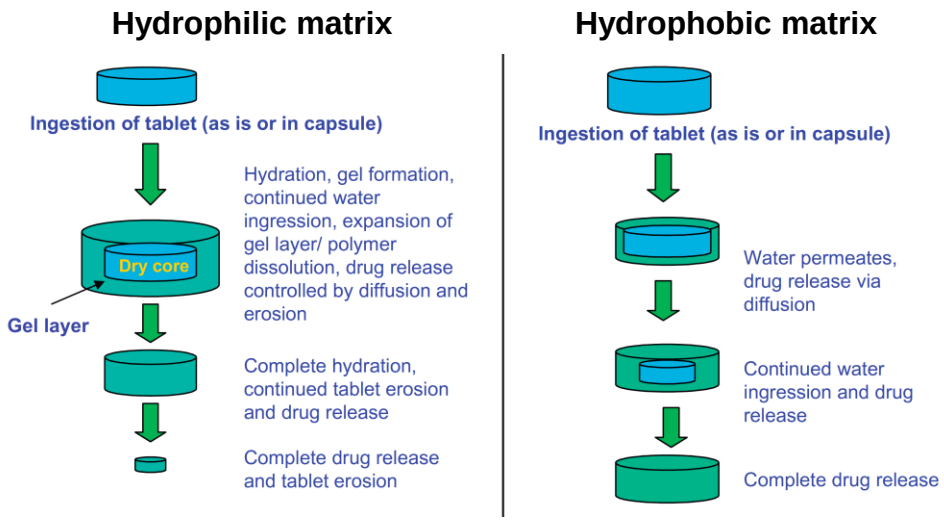
Commonly utilized oral ER systems

	Matrix	Reservoir	Osmotic pump
System	- Hydrophilic matrix - Hydrophobic matrix	- Membrane-controlled - Membrane-matrix combination	- Elementary - Microporous - Layered
Dosage Form	- Monolithic tablet - Multiparticulates (pellets/ minitablets) - Layered tablet - Compression-coated tablet	- Multiparticulates (coated pellets/ beads/ minitablets) - Monolithic tablet containing coated beads - Monolithic coated tablet	- Coated monolithic tablet - Coated layered tablet - Coated beads

Matrix ER systems

- In a matrix system, the drug substance is homogeneously mixed with the rate-controlling material(s) and other inactive ingredients to form a monolithic crystalline, amorphous, or in rare cases, molecular dispersion matrix
- Drug release occurs by diffusion from and/or erosion of the matrix system
- Based on the characteristics of the rate-controlling material, the matrix system can be divided into (a) hydrophilic and (b) hydrophobic systems

Matrix ER systems



Advantages of matrix systems

1. Capability of accommodating low and high loading of drugs having a wide range of physical and chemical properties
2. Cost-effective and easy to scale-up and manufacture
3. Suitable for in-house development since it is usually manufactured using conventional processes and equipment

- **Disadvantages**

1. A more complex design and process is required to alter release profiles or to achieve unique release patterns
2. They lack flexibility in offering multiple strengths that are usually required for Phase 1-3 clinical studies

Hydrophobic matrix systems

- In a hydrophobic inert matrix system, the drug is uniformly dissolved or dispersed throughout a matrix that involves negligible swelling or erosion of the device
- For a homogeneous monolithic matrix system containing dispersed drug, the release behavior can be described by the Higuchi equation:

$$M_t = [2D.A.C_s.t]^{1/2}$$

  - Where M_t is the drug released per unit area at time t, A is the drug loading per unit volume, C_s is drug solubility, and D is the diffusion coefficient in the matrix phase
- If the matrix is porous, then porosity and tortuosity should be taken into account

Hydrophobic matrix systems

- A simple exponential relation was introduced by Peppas to describe the general release behavior from hydrophobic nonswellable matrices:

$$Q = \frac{M_t}{M_\infty} = kt^n$$

  - Where Q is the fractional release, M_t is the drug released per unit area at time t, M_∞ is the total drug release per unit area, k is a constant, and n is the diffusional exponent
    - n = 0.5 → pure Fickian diffusional release
    - n = 1 → zero-order drug release
    - 0.5 < n < 1 → non-Fickian diffusion (anomalous transport)

Hydrophilic matrix systems

- Hydrophobic matrix systems are not suitable for insoluble drugs because the concentration gradient is too low to allow complete drug release within a reasonable time frame
- Conversely, hydrophilic matrix systems are more widely utilized because they allow a broad range of loading for drugs with low, medium, or high solubility
- The rate-controlling materials in hydrophilic matrix systems are polymers that hydrate and swell rapidly in an aqueous medium and form a gel layer on the surface of the system

Hydrophilic matrix systems

- Drug release from hydrophilic matrices involves two competing mechanisms: Fickian diffusion and matrix erosion
- Different models exist to describe drug release. The Peppas model is commonly used:

$$Q = \frac{M_t}{M_\infty} = kt^n$$

  - n = 0.5 → pure Fickian diffusional release
  - n = 1 → zero-order drug release by swelling/erosion
  - 0.5 < n < 1 → non-Fickian diffusion (diffusion + erosion)

Modulation of drug release from matrix systems

- It is difficult to obtain linear (zero-order) release kinetics especially from diffusion-controlled systems
- This can be overcome by nonuniform drug loading, multilayered systems, or mixing hydrophilic and hydrophobic matrix formers
- Weakly acidic/basic drugs may require the incorporation of buffering agents in the matrix to maintain a suitable local pH for drug release to occur at the desired rate

Reservoir ER systems

- A typical reservoir system consists of a core containing a solid drug or highly concentrated drug solution surrounded by a rate-controlling membrane
- In this design, the only structure effectively limiting the release of the drug is the polymer layer surrounding the reservoir

Reservoir ER systems

- Drug release is based on Fick's first law of diffusion:

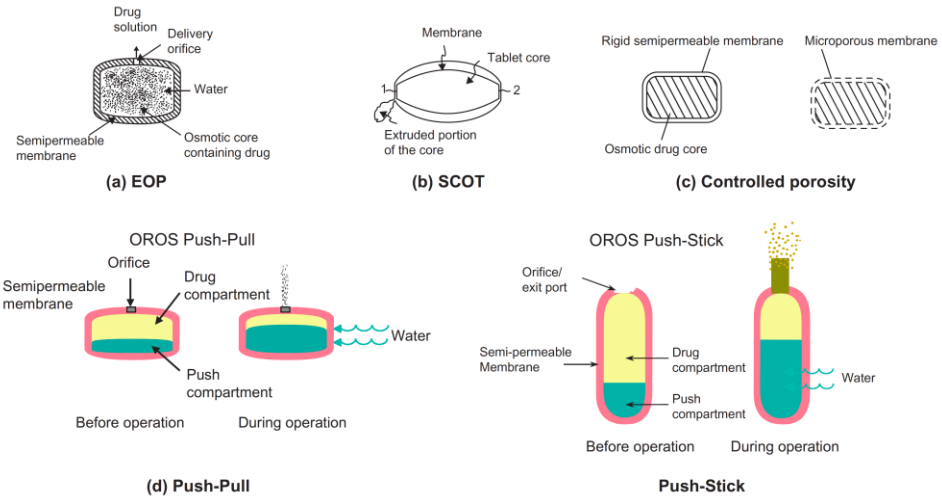
$$dM/dt = D.S.K.(C_s-C)/h$$

- Under sink conditions, a constant rate may be achieved ($M_t = k.t$)
- It is preferred to design reservoir systems as multiunits such as beads, pellets, and minitablets. Why??
- Tailored drug release can be readily obtained by combining subunits with different release characteristics
- May also require adding buffering agents to the core to obtain pH-independent drug release

Osmotic pump systems

- Similar in construction to a reservoir device but contain an osmotic agent that acts to absorb water from the surrounding medium via a semipermeable membrane
- The drug is forced out of an orifice in the device by the osmotic pressure generated by the device
- Different designs (single layer, bilayer)
- Classic osmotic pump systems offer zero-order release profile that are independent of the drug properties and release environment
- However, fabrication of this type of system often requires specialized equipment and complex processes, especially for two-chamber systems

Osmotic pump systems

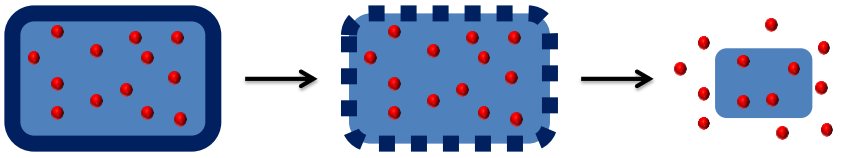


Gastro-resistant (enteric) systems

- Another variation on the membrane-controlled systems
- The membrane is designed to be disintegrated or dissolved at a certain point, e.g. change in pH
- Coating material is made of a polymer insoluble at low pH, but dissolves at higher pH (5 – 7)
- Aim to protect the drug from stomach acidity, or to protect the stomach from the drug

Gastro-resistant (enteric) systems

- Also used to target drugs to the intestines or colon, as in ulcerative colitis
- Challenges: GI pH is not always predictable and reproducible in vivo



Drug core coated with a delayed release membrane

Exposure to correct pH dissolves coating

Core dissolves and releases drug

Colon-targeted systems

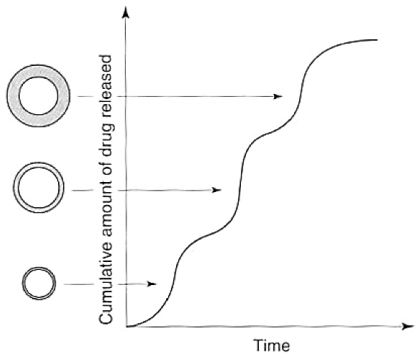
- Using pH-responsive polymers that dissolve at pH 7 (e.g. Eudragit S)
  - This is difficult to achieve due to pH changes and short residence time in the ileocecal junction
- Alternatively, gut bacteria is used to trigger drug release, e.g. azo reductase and glycosidase enzymes secreted by colonic microflora

Pulsatile release systems

- Pulsatile delivery refers to the release of a portion of the total payload in a burst followed by periods of little/ no release (lag phase) in a defined pattern
- Clinical benefits include:
  - Optimizing chronotherapy
  - Mimicking natural patterns of endogenous secretion
  - Providing optimal therapy for tolerance-inducing drugs
- Design is based on the combination of a range of formulation approaches, including single- or multiple-unit immediate and delayed release systems

Pulsatile release systems

- For example:
  - Drug is divided into smaller release units (spherical granules)
  - Each unit is coated with a slowly dissolving coat with varying thickness
  - Release units with different release times are mixed and formed into a disintegrating tablet



Rational design of MR systems

1. Identify the clinical need and define target in vivo product performance
2. Thoroughly assess feasibility of MR delivery which includes:
   - Characterization of API physicochemical and biopharmaceutical properties, dose, regional absorption, in vivo disposition and pharmacodynamics
   - PK simulation to calculate theoretical drug input rate and its range required to produce the desired plasma concentration-time profile
3. Select an appropriate MR technology

Factors affecting the feasibility of developing oral modified release systems

1. Solubility/dose
   - Low solubility combined with high dose may limit the suitability for developing an MR system
   - Drug absorption is usually more variable or incomplete when the in vivo release occurs past the ileocecal junction
   - In some cases, apparent absorption of poorly soluble drugs may be inherently prolonged due to the slow dissolution of the drug particles
2. Stability
   - Drugs must be stable to pH, enzymes and flora throughout the entire intended delivery regions of the GI tract
   - For example, a drug subject to degradation by the colonic microflora is not a suitable candidate for MR delivery that requires an in vivo absorption for > 5-6 hours post dosing

Factors affecting the feasibility of developing oral modified release systems

3. Lipophilicity/permeability
   - Absorption of BCS class III or IV drugs may be limited by permeability that also differs with regions of the GIT
   - Altering the release of such drug substances in the lower GIT typically has little effects on the shape of PK profiles and usually result in lower absorption when > 5-6 hours of in vivo absorption is required
4. Elimination $t_{1/2}$
   - The need for ER systems is often a result of short half-life. However, other variables (e.g. MEC, V_d, dose) are also Important in determining ER feasibility
   - Hence, developing a twice-daily (or once-daily) system may be possible for one compound, but not feasible for another drug having similar half-lives

Factors affecting the feasibility of developing oral modified release systems

5. Therapeutic window
   - For drugs with relatively short half-lives, the lower the MEC and the higher the minimum toxic concentration (MTC), the more Likely it is to achieve prolonged drug exposure above MEC using higher dose. However, this will result in a greater fluctuation in steady-state plasma levels that is often undesirable for narrow therapeutic index drugs
6. First-pass metabolism
   - For drugs with saturable first-pass metabolism (hepatic or gut), bioavailability may be compromised due to slow drug release from an ER system
7. PK-PD relationship
   - The relationship between drug concentration (C) and the pharmacological effect (E) plays a critical role in determining rationale and need for MR delivery

Choosing an appropriate MR technology

System	Advantages	Disadvantages
Hydrophilic matrix	Suitable for compounds with a wide range of properties and low to high drug loading Generally robust formulation and process when rationally designed Use of conventional manufacturing equipment and process Cost effective: Shorter development time and lower cost Release kinetics and profiles can be tailored with modification Multiunits possible	Drug release often sensitive to test conditions Less flexibility to adjust dose strengths for single-unit system Increased formulation/process complexity to achieve tailored drug release (layered or compression coated system)
Hydrophobic matrix	Suitable for soluble compounds and low to high drug loading Use of conventional manufacturing equipment and process Release kinetics and profiles can be tailored with modification Multiunits possible	Not applicable to compounds with low solubility Nonzero-order release Propensity for incomplete drug release Drug release often sensitive to processing and test conditions Less flexibility to adjust dose strengths for single-unit system Increased formulation/process complexity for tailored drug release (layered or compression coated system)

Choosing an appropriate MR technology

System	Advantages	Disadvantages
Multiunit reservoir	Readily tailored release kinetics and profiles (eg, zero-order, pulsatile, biphasic, colonic) Minimized risk of dose dumping and local irritation Lower in vivo variability owing to favorable GI transit properties More consistent in vivo performance Easy dose adjustment: Single formulation amenable to multiple strengths Suitable for pediatric/geriatric use Use of conventional manufacturing equipment and process	Only applicable to compounds with relatively high solubility Drug release often sensitive to test conditions Limited drug loading Process development and scale-up more challenging
Osmotic pump	Applicable to compounds with a relatively wide range of properties Drug release generally independent of drug properties and test conditions Zero-order release	Limited drug loading Ghost tablets Delayed onset (1-2 h) and/or incomplete drug release Solvent-based process Lengthy, complex and inefficient manufacturing processes and control (eg, Layered tablet) Specialized equipment, facility Highest development and manufacturing cost and time

Case studies

- Hu, Manyu, et al. "Exploring the Potential of Hydrophilic Matrix Combined with Insoluble Film Coating: Preparation and Evaluation of Ambroxol Hydrochloride Extended Release Tablets." *AAPS PharmSciTech* 21.3 (2020): 1-9
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